

Application No. 10/534,079
Paper Dated: September 27, 2010
In Reply to USPTO Correspondence of May 25, 2010
Attorney Docket No. 0470-051409

REMARKS

Claims 32-73 are pending in the above captioned application. Claims 49-73 have been withdrawn as directed to non-elected subject matter. Claims 32-48 stand rejected under 35 U.S.C. § 112, second paragraph, and § 103. Additionally, the Examiner has objected to claim 35 as being substantially duplicative to claim 32. In view of the amendments to the claims and remarks below, Applicants respectfully request that this rejection be reconsidered and withdrawn.

35 U.S.C. § 112, Second Paragraph

Claims 32-48 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because claim 32 recites “a protecting group C,” which the Examiner contends is confusing since “C” is the chemical symbol for carbon. Although Applicants respectfully disagree because claim 32 defines C as a protecting group, Applicants have nevertheless amended claim 32 to recite “Cp” instead of “C” for the protecting group.

Claim 41-43 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because claims 41 and 42 use the abbreviation “PVP”. Applicants have amended claims 41 and 42 to recite “polyvinylpyridine (PVP).”

Accordingly, withdrawal of these rejections is respectfully requested.

35 U.S.C. § 103

Claims 32-38, 40 and 46-48 stand rejected as being obvious over Suzuki et al., (Steroids (1995) 60: 277-285) (“Suzuki”) in view of Poirier (Tetrahedron (1991) 47: 7751-7766) (“Poirier”) as evidenced by GREENE’S PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3E (1999) (“Greene”). Claims 32-40 and 46-48 stand rejected as being obvious over Suzuki and Poirier as evidenced by Greene in further view of Pearlman (U.S. Pat. No. 4,739,078). Claims 32-38 and 40-48 stand rejected as being obvious over Suzuki and Poirier as evidenced by Greene in further view of Cainelli (Synth. Comm. Pp. 45-47 (1989) (“Cainelli”).

The invention, as recited in claim 32, is directed to a process for the preparation of estra-1,3,5 (10)-trien-3,15 α , 16 α , 17 β -tetraol (1). The process comprises converting estrone (7) into 3-A-oxy-estra-1,3,5(10), 15-tetraen-17-one (6), wherein A is a protecting group. The 17-keto group of 3-A-oxy-estra-1,3,5(10), 15-tetraen-17-one (6) to 3-A-oxy-estra-1,3,5(10), 15-tetraen-17 β -ol (5) is reduced. The 17-OH group of 3-A-oxy-estra-1,3,5(10), 15-tetraen-17 β -ol (5) to 3-A-oxy-17-Cp-oxy-estra-1,3,5(10), 15-tetraene (4), wherein Cp is a protecting group is protected. The carbon-carbon double bond of ring D of 3-A-oxy-17-Cp-oxy-estra-1,3,5(10), 15-tetraene (4) to protected estetrol (3) is oxidized. The protecting group is removed. First, protecting group A is removed first to form 17-OC protected estetrol (2). Subsequently protecting group Cp is removed to form estetrol (1). The protecting group A is selected from the group consisting of a C₁-C₅ alkyl group and a C₇-C₁₂ benzylic group. The protecting group Cp is selected from monofunctional aliphatic hydroxyl protecting groups.

Suzuki also discloses the synthesis of estetrol by using a compound disclosed by Nambara *et al.* (Steroids (1976) 27: 111-121) as starting material. The carbonyl group at C₁₇ of this compound was first reduced followed by acetylation yielding estra-1,3,5(10),15-tetraene-3,17-diol-3,17-diacetate. The latter was subjected to oxidation with OsO₄ which provided estra-1,3,5(10)-triene-3,15 α ,16 α ,17 β -tetraol-3,17-diaceta the in 46% yield. According to Nambara and Suzuki, the synthesis of estetrol can be performed with a yield of approximately 8% starting from estrone.

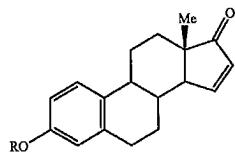
Problems occur when upscaling the method disclosed in Suzuki. Particularly, the acetylene protecting group in Suzuki used to protect the 3-OH group and/or the 17-OH afforded a low selectivity under the conditions of further reaction steps thereby giving rise to the formation of an unacceptable level of side products. Suzuki's acetyl protecting group also hampers purification steps because it is relatively susceptible to hydrolysis and solvolysis when a protic solvent, such as methanol, is used.

The present invention solves the technical problems observed when practicing Suzuki's method. Namely, by using a more stable protecting group for the 3_OH group of

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estetrol, a higher yield and purer product can be obtained in comparison to the method used by Suzuki.

Poirier, which pre-dates Suzuki, discloses the following compound:



Since Poirier pre-dates Suzuki, one would assume that Suzuki was aware of the compounds disclosed in Poirier, yet did not use or suggest using the above-identified compound in its method.

Greene discloses a large group of possible protecting groups for OH-groups.

In order to establish a *prima facie* case of obviousness, the Examiner must provide some reason why one would combine the references in the manner as recited in the claims. Here, the Examiner acknowledges that Suzuki does not disclose a 3-OH protecting group A as recited in claim 32. However, the Examiner contends that Poirier discloses such a protecting group. The mere disclosure of protecting group A in Poirier does not make it obvious to use the protecting group in Suzuki's method. If it was obvious, one would have expected Suzuki to use protecting group A because, as discussed below, the recited invention provides unexpectedly improved results over the method disclosed in Suzuki. Since Suzuki, who presumably knew about a group that was disclosed before Suzuki published its method, was not used, and this group provides unexpectedly improved results, the failure of Suzuki to disclose the use of this group suggests that the invention is not obvious.

Moreover, the rejection is predicated on the total synthesis of estretrol from estrone. However, claim 32 and the claims depending therefrom are directed to a process, and thus, the individual steps and combination of the steps must be considered. Hence, *inter alia*, it is important to consider when the protecting group is introduced and removed.

Suzuki teaches that both the 3-OH and the 17-OH groups are acetylated after the reduction with LiAlH₄ (Office Action at pages 10-11). In contrast, claim 32 recites that the 17-OH group is acetylated after the reduction step. Thus, Suzuki, alone or in combination with the other cited references, does not teach or suggest the recite order of when the 3-OH and 17-OH groups are protected.

Furthermore, there is no motivation to modify the 3-O-acetate group into a benzyloxy or methoxy group. The Examiner contends that one would be motivated to modify the 3-O-acetate (estate) protecting group disclosed by Suzuki with one taught by Poirier because “methyl and benzyl ethers would be expected to function as effective as 3-OH protecting groups” (Office Action at pages 12-13). Poirier discloses compounds 8 and 9 in scheme 1 which correspond to compound 4 disclosed in scheme 4 in the above-captioned application. However, Poirier’s compounds 8 and 9 are not subjected to a reduction step to form an enol, whereas, in the recited invention, compound 6 (for example) is reduced to an enol.

Moreover, step 5 in claim 32 recites “removing the protecting groups, wherein protecting group A is removed first to form 17-OC protected estetrol (2) and subsequently protecting group Cp is removed to form estetrol (1).” Thus, not only do the claims recite a specific sequence of protecting the OH groups, they also recite a specific sequence of removing them. There is no reason why one would use this specific sequence.

Moreover, even if a *prima facie* case of obviousness was set forth, the rejection is rebutted by the unexpected results. Suzuki’s method results in yields of only about 8%, whereas the recited invention has yields of at least 10% (Application at page 6, lines 5-9).

For these reasons, Applicants respectfully request that the rejections asserted against claim 32 be reconsidered and withdrawn. Since claims 33, 34 and 36-48 depend directly or indirectly to claim 32, Applicants respectfully request that the rejections asserted against these claim likewise be reconsidered and withdrawn for the reasons discussed above.

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Objection to Claim 35

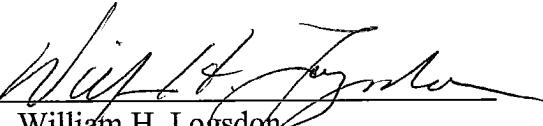
In view of the cancellation of claim 35, the objection asserted against this claim is now moot.

CONCLUSION

In view of the amendments to the claims and remarks above, Applicants respectfully request that the rejections and objection asserted in the Office Action of May 25, 2010 be reconsidered and withdrawn, that pending claims 32-34 and 36-48 be allowed and that withdrawn claims 49-73 be rejoined.

Respectfully submitted,
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